Full Text PA-97-100

REGULATION OF THE IMMUNE RESPONSE

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National Institute of Allergy and Infectious Diseases
National Institute on Aging
National Institute of Diabetes and Digestive Diseases and Kidney Diseases
National Institute of Arthritis and Musculoskeletal and Skin Diseases

PURPOSE

The National Institute of Allergy and Infectious Diseases (NIAID), the National Institute on Aging (NIA), the National Institute of Diabetes and Digestive and Kidney Disease (NIDDK), and the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), National Institutes of Health (NIH), invite applications to enhance our knowledge of mechanisms that control the immune response, age- related changes in the regulation of immune responses, and theunderlying mechanisms responsible for these changes. Enhanced knowledge in these areas is needed for the generation and control of immune responses to antigenic challenges and for the development of new strategies to treat and prevent immunologically based diseases. Support will be provided for basic and pre-clinical studies using molecular and cellular approaches to dissect the immune response.

HEALTHY PEOPLE 2000

The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2000," a PHS-led national activity for setting priority areas. This Program Announcement (PA), "REGULATION OF THE IMMUNE RESPONSE", is

related to the priority areas of Immunization and Infectious Diseases and Diabetes and Chronic Disabling Disease. Potential applicants may obtain a copy of "Healthy People 2000" (Full Report: Stock No. 017-001-00474-0 or Summary Report: Stock No. 017-001-00473-1) through the Superintendent of Documents, Government Printing Office, Washington, DC 20402-9325 (telephone 202-512-1800).

ELIGIBILITY

Applications may be submitted by for profit and non-profit organizations, public and private, such as universities, colleges, hospitals, laboratories, units of State and local governments, and eligible agencies of the Federal government. Domestic and foreign institutions are eligible to apply for R01 grants. Foreign institutions are not eligible for First Independent Research Support and Transition (FIRST) awards. Racial/ethnic minority individuals, women, and persons with disabilities are encouraged to apply as Principal Investigators.

MECHANISMS OF SUPPORT

Traditional research project grant (R01) and FIRST (R29) applications may be submitted in response to this PA. Applications for R01 grants may request up to five (5) years of support; applications for R29 grants must request five years of support.

Responsibility for the planning, direction, and execution of the proposed research for all applicable mechanisms of support will be solely that of the applicant.

RESEARCH OBJECTIVES

Background

Investigation is needed to enhance understanding of the activation of signaling pathways in immune system cells, the development of effector cell specificity, phenotype and function, and processes involved in the overall regulation of immune responses. For example, the molecular control of immunoglobulin gene expression and gene recombination has progressed significantly with the identification of enhancer elements, switch recombination sequences and immunoglobulin germline heavy chain transcription from cryptic promoters. The finding that the same molecular machinery used for immunoglobulin gene recombination is also used for the T-cell receptor gene recombination shows economy of the system. However, it has been

demonstrated that the intracellular and external regulatory signals that trigger and control the recombination processes in the two systems are different.

While many components of immune cell regulation have been discovered, including pathways of antigen processing and subsequent Major Histocompatibility Complex (MHC) association as well as the activities of cytokines, chemokines and growth factors, the complexity of the emerging picture suggests that many regulatory processes are still unknown. One example is how signals from the surface of immune cells are differentially interpreted to lead to either stimulation or suppression of immune function. Little is known about how the immune system is influenced by and interacts with other systems, including the endocrine and nervous systems. It is expected that continued support of immunological research will ensure further progress leading to a better understanding of the immune system.

Research Objectives and Scope

The major objective of this PA is to continue support for research to elucidate the molecular machinery and control of the immune response at all levels. This includes support for molecular biological studies on gene expression, gene recombination and interactions among different parts of the immune system to control the overall response to a stimulus. The scope of research to be supported under this PA includes, but is not limited to, the following broad areas of interest and specific examples of investigations.

o definition of pathways that regulate gene activation and intra- or extra-cellular signals that control gene rearrangements in the immune system;

o elucidation of the control of the immune system antigen receptor repertoire to prevent autoimmune reactivity;

o further definition of interactions of immune system molecules to initiate and maintain an effective immune response;

o continued mapping of genes activated in cells of the immune system;

o further definition of the processes that control immune cell differentiation and development;

o determination, at the cellular and molecular levels, of the central nervous system modulation of the immune response;

o determination of the role of bidirectional signaling between T cells, B cells, antigen presenting cells and other immune system cells in normal and abnormal immune responses;

o elucidation of the function of antigen processing, presentation and costimulation in establishing the local microenvironment necessary for activation and establishment of effector functions; and

o elucidation of the cellular and molecular bases of age-related changes in immune regulation.

INCLUSION OF WOMEN AND MINORITIES IN RESEARCH INVOLVING HUMAN SUBJECTS

It is the policy of the NIH that women and members of minority groups and their subpopulations must be included in all NIH supported biomedical and behavioral research projects involving human subjects, unless a clear and compelling rationale and justification are provided that inclusion is inappropriate with respect to the health of the subjects of the purpose of the research. This policy results from the NIH Revitalization Act of 1993 (Section 492B of Public Law 103-43).

All investigators proposing research involving human subjects should read the "NIH Guidelines for Inclusion of Women and Minorities as Subjects in Clinical Research", which have been published in the Federal Register of March 28, 1994 (FR 59 14508-14513) and the NIH Guide for Grants and Contracts, Vol. 23, No.11, March 18, 1994.

Investigators may obtain copies from these sources or from the program staff listed under INQUIRIES. Program staff may also provide additional relevant information concerning the policy.

APPLICATION PROCEDURES

Applications are to be submitted on the grant application for PHS 398 (rev. 5/95) and will be accepted on the standard application deadlines as indicated on the application kit. Application kits are available at most institutional offices of sponsored research and may be obtained from the Division of Extramural Outreach and Information Resources, National Institutes of Health, 6701 Rockledge Drive, MSC 7910, Bethesda, MD 20892-7910, telephone (301) 435-0714, email: asknih@odrockm1.nih.gov.

For purposes of identification and processing, item 2 on the face page of the application must be marked "YES". The PA number and the PA title must also be typed in section 2.

The completed, signed original and five (5) legible, single-sided copies of the application must be sent or delivered to:

DIVISION OF RESEARCH GRANTS
NATIONAL INSTITUTES OF HEALTH
6701 ROCKLEDGE DRIVE, ROOM 1040, MSC 7710
BETHESDA, MD 20892-7710
BETHESDA, MD 20817-7710 (for express/courier service)

R29 applications must include at least three (3) sealed letters of reference attached to the face page of the original application. FIRST applications submitted without the required number of reference letters will be considered incomplete and will be returned without review.

Applicants from institutions that have a General Clinical Research Centers (GCRC) funded by the NIH National Center for Research Resources may wish to identify the Center as a resource for conducting the proposed research. If so, a letter of agreement from the GCRC Program Director must be included in the application material.

REVIEW CONSIDERATIONS

Review Procedures

Applications will be assigned on the basis of established PHS referral guidelines. Upon receipt, applications will be reviewed for completeness by the NIH Division of Research Grants. Incomplete applications will be returned to the applicant without further consideration. Applications will be reviewed for scientific and technical merit by study sections of the Division of Research Grants, NIH, in accordance with the standard NIH peer review procedures.

As part of the initial merit review, all applications will receive a written critique and undergo a process in which only those applications deemed to have the highest scientific merit, generally the top half of the applications under review, will be discussed, assigned a priority score, and receive a second level review by the appropriate national advisory council.

Review Criteria

The five criteria to be used in the evaluation of grant applications are listed below. To put those criteria in context, the following information is contained in instructions to the peer reviewers.

The goals of NIH-supported research are to advance our understanding of biological systems, improve the control of disease, and enhance health. The reviewers will comment on the following aspects of the application in their written critiques in order to judge the likelihood that the proposed research will have a substantial impact on the pursuit of these goals. Each of these criteria will be addressed and considered by the reviewers in assigning the overall score weighting them as appropriate for each application. Note that the application does not need to be strong in all categories to be judged likely to have a major scientific impact and thus deserve a high priority score. For example, an investigator may propose to carry out important work that by its nature is not innovative but is essential to move a field forward.

1. Significance. Does this study address an important problem? If the aims of the application are achieved, how will scientific knowledge be advanced? What will be the effect of these studies on the concepts or methods that drive this field?

2. Approach. Are the conceptual framework, design, methods, and analyses adequately developed, well-integrated, and appropriate to the aims of the project? Does the applicant acknowledge potential problem areas and consider alternative tactics?

3. Innovation. Does the project employ novel concepts, approaches or method? Are the aims original and innovative? Does the project challenge existing paradigms or develop new methodologies or technologies?

4. Investigator. Is the investigator appropriately trained and well suited to carry out this work? Is the work proposed appropriate to the experience level of the principal investigator and other researchers (if any)?

5. Environment. Does the scientific environment in which the work will be done contribute to the probability of success? Do the proposed experiments take advantage of unique features of the scientific environment or employ useful collaborative arrangements? Is there evidence of institutional support?

The initial review group will also examine: the appropriateness of proposed project budget and duration; the adequacy of plans to include both genders and minorities and their subgroups as

appropriate for the scientific goals of the research and plans for the recruitment and retention of subjects; the provisions for the protection of human and animal subjects; and the safety of the research environment.

AWARD CRITERIA

Applications will compete for available funds with all other favorably recommended applications. The following will be considered when making funding decisions: quality of the proposed project as determined by peer review, program balance, and availability of funds.

INQUIRIES

Written and telephone inquiries are encouraged. The opportunity to clarify any issues or questions from potential applicants is welcome.

Inquiries regarding programmatic (research scope and eligibility) issues may be directed to:

Stephen M. Rose, Ph.D.
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Division of Allergy, Immunology and Transplantation
National Institute of Allergy and Infectious Diseases Solar Building,
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National Institute on Aging
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Walter S. Stolz, Ph.D.
Director, Division of Extramural Activities
National Institute of Diabetes and Digestive and Kidney Diseases
National Institutes of Health
Natcher Building, Room 6As-25C
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Susana Serrate-Sztein, M.D.
Chief, Arthritis Branch
National Institute of Arthritis and Musculoskeletal and Skin Diseases
Natcher Building, Room 5AS37G
Telephone: (301) 594-5032
FAX: (301) 480-4543
Email: szteins@ep.niams.nih.gov

Direct inquiries regarding fiscal matters to:

Laura Eisenman
Division of Extramural Activities
National Institute of Allergy and Infectious Diseases Solar Building,
Room 4B23
6003 Executive Blvd.
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Telephone: (301) 496-7075
FAX: (301) 480-3780
Email: le55d@nih.gov

Mr. Joseph Ellis
Grants Management Officer
Grants and Contracts Management Office
National Institute on Aging
Gateway Building, Suite 2N212
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FAX: (301) 402-3672
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Nancy Dixon
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email: dixonn@ep.niddk.nih.gov

Ms. Carol Fitzpatrick
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AUTHORITY AND REGULATIONS

This program is supported under authorization of the Public Health Service Act, Sec. 301(c), Public Law 78-410, as amended. The Catalogue of Federal Domestic Assistance Citation is No. 93.855 - Immunology, Allergy, and Transplantation Research, No. 93.366 -Aging Research, No. 93.847 - Digestive Diseases and Nutrition, No. 93.848 - Diabetes, Endocrinology and Metabolic Diseases, No. 93.849 -Kidney, Urologic and Hematologic Diseases, and No. 93.846 -Arthritis, Musculoskeletal and Skin Diseases Research. Awards will be administered under PHS grants policies and Federal Regulations 24 CFR Part 52 and 45 CFR Part 74. This program is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems review.

The PHS strongly encourages all grant and contract recipients to provide a smoke-free workplace and promote the non-use of all tobacco products. In addition, Public Law 103-227, the Pro-

Children Act of 1994, prohibits smoking in certain facilities (or in some cases, any portion of a facility) in which regular or routine education, library, day care, health care or early childhood development services are provided to children. This is consistent with the PHS mission to protect and advance the physical and mental health of the American people.

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